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Partial Trisomy 17q22-qter and Partial Monosomy Xq27-qter in a Girl With a De Novo Unbalanced Translocation Due to a Postzygotic Error: Case Report and Review of the Literature on Partial Trisomy 17qter

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Partial trisomy 17q22-qter is a rare but well-recognized clinical entity. We present a case of partial trisomy for the long arm of chromosome 17, which was detected in a female infant with severe psychomotor and somatic retardation, Stargardt disease, short limbs, and numerous minor anomalies. Differential chromosomal staining demonstrated an excess of genetic material on the long arm of the late replicating X chromosome. FISH and DNA polymorphism analysis showed that the extra material belonged to the distal part of the long arm of chromosome 17 and that there was a partial monosomy of the distal part of the long arm of the derivative X chromosome. The breakpoint regions of this translocation were identified by molecular analysis using polymorphic microsatellite markers on human chromosomes 17 and X. The origin of the abnormal X chromosome was found to be paternal, whereas the origin of the duplicated part of chromosome 17 was maternal. The unbalanced translocation between the paternal X and the maternal chromosome 17 is, therefore, suggested to be due to a postzygotic error. Am. J. Med. Genet. 70:87–94, 1997.

KEY WORDS: chromosome 17; partial trisomy 17q; de novo unbalanced translocation; postzygotic error; Stargardt disease

INTRODUCTION

Abnormalities of chromosome 17 are relatively uncommon, apart from those found in leukemias such as chronic myelocytic leukemia frequently showing an isochromosome 17q during the blastic crisis [Nakagawa et al., 1992]. Complete trisomy 17 has been recorded in spontaneous abortions but with an extremely low incidence, suggesting that nondisjunction of chromosomes 17 occurs rarely, or that the loss of such conceptuses occurs in early unrecognized pregnancies [Warburton et al., 1980].

Until now, 28 liveborn cases and two prenatal diagnoses of partial trisomy for the distal region of 17q were reported. Most of these were due to adjacent-1 segregation of reciprocal translocations, which were derived from either one of the parents [Hagemeijer et al., 1977; Berberich et al., 1978; Turleau et al., 1979; Yamamoto et al., 1979; Gallien et al., 1981; Shawe et al., 1983; Naccache et al., 1984; Bridge et al., 1985; Robb et al., 1987; Lenzini et al., 1988; Caine et al., 1989; Ohdo et al., 1989; Cotter and Stewart, 1990; Nunez et al., 1993]. Three cases were due to a familial chromosome 17 inversion [Greenberg et al., 1986; Kingston et al., 1996]. A few were de novo events [Fryns et al., 1979; Parcheta et al., 1985; King et al., 1991]. Another previous case of trisomy 17q was interpreted as the result of tandem duplication of band 17q25 largely on the grounds of clinical findings [Orye and Van Bever, 1985]. Shimizu et al. [1988] reported the first known case of inverted tandem duplication of 17q24-q25 of de novo origin. Mosaicism regarding direct duplication 17q also has been reported recently in a liveborn infant

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[Serotkin et al., 1988], as well as in a fetus during prenatal diagnosis where the abnormality developed after differentiation of embryonic and trophoblastic cells [King et al., 1991]. Salamanca-Gomez and Armendares [1975] have reported the first case of trisomy 17q due to isochromosome 17q.

Duplication of the distal portion of 17q is apparently quite rare. The reported cases have involved bands q21, q22, q23, q24, q25-qter [Hagemeijer et al., 1977; Berberich et al., 1978; Fryns et al., 1979; Turleau et al., 1979; Gallien et al., 1981; Shawe et al., 1983; Naccache et al., 1984; Bridge et al., 1985; Orye and Van Bever, 1985; Parcheta et al., 1985; Greenberg et al., 1986; Robb et al., 1987; Lenzini et al., 1988; Serotkin et al., 1988; Shimizu et al., 1988; Caine et al., 1989; Ohdo et al., 1989; Cotter and Stewart, 1990; King et al., 1991; Nunez et al., 1993; Kingston et al., 1996]. Identification of additional material on a chromosome by cytogenetic techniques alone is often difficult when the extra material cannot be traced to a parental balanced translocation. The smaller the length of extra material, the more difficult becomes the problem of identification. Chromosomal aberrations involving small segments of chromosomes often create serious diagnostic problems.

We present the clinical details of a girl with partial trisomy of the distal part of 17q and partial monosomy of the distal part of Xq. Use of FISH and DNA analysis permitted the identification of the chromosome 17 and X breakpoint regions and completed the cytogenetic evaluation.

CLINICAL REPORT

The proposita (Fig. 1) was born to healthy, nonconsanguineous parents who already had a healthy daughter. There were no previous miscarriages. Table I shows the physical measurements. There was a single umbilical artery. The patient was referred at 10 days because of minor anomalies and was re-evaluated at the ages of 2 6/12 and 3 4/12 years. The examinations demonstrated psychomotor retardation, muscular hypotonia, short stature with rhizomelic limb shortness hirsutism, very wide anterior fontanelle, frontal bossing, temporal "retraction," facial and cranial asymmetry, widow's peak, hypertelorism, upslanted palpebral fissures, broad and depressed nasal bridge, broad and short nose, poorly delineated philtrum, wide mouth with thin lips, downturned corners of the mouth, apparently low-set, posteriorly angulated, malformed ears, micro-retrognathia, very low posterior hairline with short and webbed neck, widely spaced nipples, and anteriorly placed anus. Table II shows the psycho-

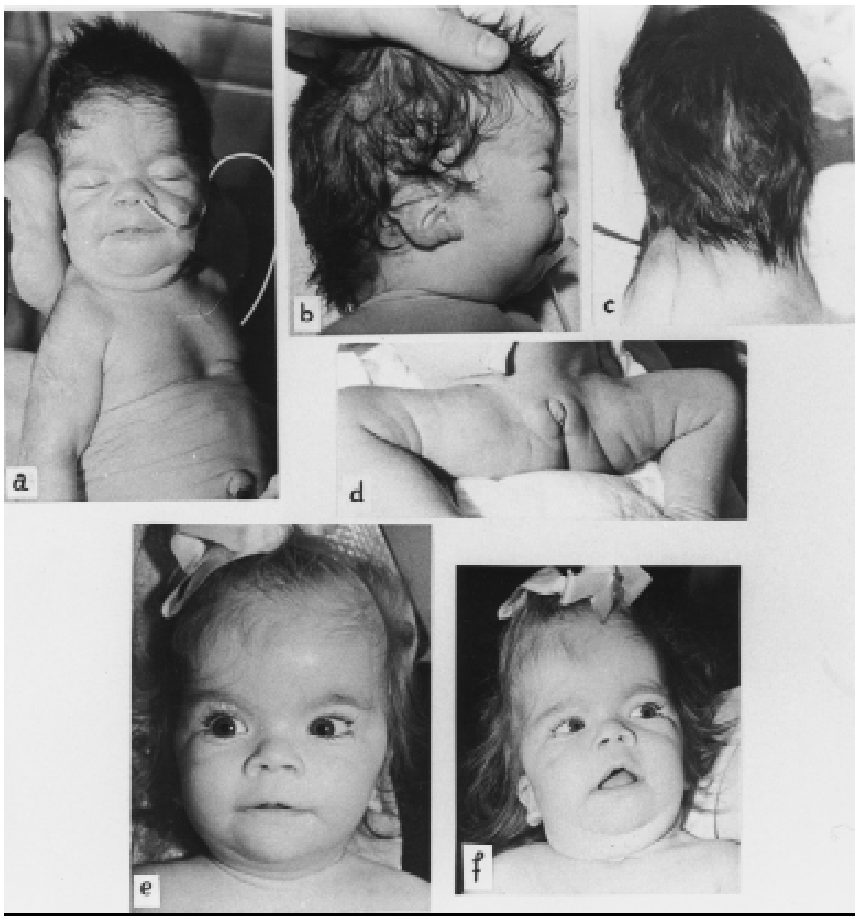

Fig. 1. Clinical photographs of the proposita with partial trisomy 17q. **a–d**: At 10 days of age (notice hirsutism, skin laxity, low set-posteriorly rotated-malformed ear, clitoris hypertrophy. **e and f:** At 13 months of age (frontal bossing, widow's peak, hypertelorism, broad nasal bridge, wide mouth, thin upper lip, corners of the mouth).

TABLE I. Physical Measurements of a Child With Partial Trisomy 17q*

	Birth	10 days	2 6/12 years	3 4/12 years
Weight (g)	2,940 (25th centile)	NM	10.100 (3rd centile)	11.680 (3rd centile)
Length (cm)		49.5 (25th centile)	82.5 (3rd centile)	86.5 (3rd centile)
Head circumference (cm)		34.5 (50th centile)	NM	47.0 (3rd centile)
Fontanelle		8 × 8.5 (»3rd SD)	4.5 × 5.5	2.2 × 4.3
Span		NM	78	NM
Lower segment		NM	36 (normal)	NM
Chest circumference		33 (50th centile)	NM	NM
Internipple distance		9.7 (97th centile)	NM	NM
Sternum		6 (–1 SD)	NM	NM
Palm length		NM	5.6 (3rd centile)	NM
Middle finger length		NM	4.0 (3rd centile)	NM
Foot length		NM	11.2 (‹3rd centile)	NM

*NM = not measured; SD = standard deviation.

motor development. The first teeth erupted at 20 months.

Ophthalmologic examination at 2 years showed Stargardt maculopathy. Results of the laboratory investigations were normal with the exception of G6PD enzyme which was only ~10% (32U/10^{12}RBC) of the normal value (146–376U/10^{12}RBC). Analysis of the G6PD enzyme in the parents showed partial deficiency in the mother (112U/10^{12}RBC) and normal value in the father (210U/10^{12}RBC).

CYTOGENETIC ANALYSIS

Chromosome analysis was carried out on standard PHA-stimulated blood cultures. The following banding techniques were applied to air-dried slides: RHG, high resolution GTG banding, and QFQ, according to the nomenclature [ISCN, 1995]. The replication pattern of the X chromosome was studied using the BrdU-pulse (RTBG) technique. With this technique, late replicating chromosomes appear more elongated and less contrasted than the early replicating ones.

TABLE II. Psychomotor Development of a Child With Partial Trisomy 17q

Milestones	Years (if not otherwise defined)
Head support	2 10/12 (partially)
Rolls over	2 4/12
Ability to sit	Not yet
Tries to get up to sit position	3 3/12
Stays with support	2 11/12
Creeping	Not yet
Parachute reactions	Not yet
Generalized hypotonia	Persists
Follows with the eyes	2 11/12
Conjugate eye movements	Not always
Social smile	2 10/12
Turns to voice	3 1/12
Cries out with pleasure	3 3/12
Repetitive vowel and consonant sounds	Never
Imitation of sounds/word repeat	2 11/12
Four words with meaning	2 6/12
Brings objects to the mouth	7–8 months
Reaches for object	1 4/12
Passes from hand to hand	1 4/12
Bangs 2 cubes held in hands	3 4/12
Claps the hands	2 6/12
Waves “bye-bye”	3 4/12
Releases an object upon request	Not yet
Follows simple instructions	Not yet
Chewing	Not yet
Sphincter control	Not yet

FLUORESCENCE IN SITU HYBRIDIZATION

FISH was done using commercially available biotin-dUTP labelled probes according to the manufacturer's instructions. Whole chromosome paint 17 and X (Cambio) and 17p telomere cosmid probe (Oncor) were used.

TABLE III. Microsatellite DNA Markers From Chromosomes 17 and Xq in a Child With a De Novo Unbalanced Translocation and in Her Parents*

	Genotypes		
Locus	Fa	Mo	Prob
D17S849	13	12	23
D17S804	12	22	22
D17S799	13	23	13
D17S783	12	12	11
D17S798	12	22	12
D17S800	13	12	11
D17S806	11	23	12
D17S788	13	23	133
D17S809	23	13	333
D17S787	22	13	112
D17S808	12	12	122
D17S794	13	22	223
D17S789	13	12	111
D17S801	12	33	133
D17S784	11	11	111
DXS995	1	21	12
DXS1002	1	22	12
DXS990	2	12	22
DXS1106	3	12	23
DXS1072	1	11	11
DXS1210	3	12	23
DXS984	1	11	1/11
DXS1227	2	12	1
DXS1193	3	12	1
G6PD	1	11	1/11
F8	1	12	2

*The loci on chromosomes 17 and X are ordered in columns corresponding to their relative order based on linkage analysis [Gyapay et al., 1994]. The last two loci in the X chromosome column (G6PD and F8) are not incorporated in the genetic linkage map, but are physically localised to Xqter. The three genotypes correspond to father, mother, and proband, respectively. The numbers in the genotypes represent the different alleles at a specific locus.

The biotin-labelled probes were detected with FITC (fluorescein isothiocyanate)-conjugated avidin (Vector Laboratories), and amplified by two rounds of biotinylated anti-avidin antibodies (Vector Lab), and the chromosomes were counterstained with DAPI and propidium iodine. Preparations were mounted in antifading agent (Perma Fluor, Immunon) and observed under a fluorescence microscope (filter combination Zeiss 4302295).

MOLECULAR ANALYSIS

For molecular analysis, polymorphic microsatellite DNA markers from human chromosomes 17 and X were used (Table III). Genomic DNA was extracted from EDTA-anticoagulated blood by a salting-out procedure [Miller et al., 1988]. Primers flanking microsatellites on human chromosomes 17 and Xqter were as published elsewhere [Gyapay et al., 1994; Lalloz et al., 1991; Theune et al., 1991]. Polymerase chain reaction (PCR) amplification of genomic DNA with end-labeling of primer, polyacrylamide gel electrophoresis of the amplification products, and autoradiography were performed according to protocols published previously [Economou et al., 1990; Petersen et al., 1990]. The scoring of polymorphic alleles was done as described elsewhere [Petersen et al., 1991].

RESULTS

Cytogenetic analysis showed 46 chromosomes in all cells. One of the X chromosomes was found to be abnormal: at the distal end of the long arm a small segment of extra material was present (Fig. 2a). The X-segment of the rearranged chromosome was late replicating in R-banded preparations following BrdU incorporation, but the distal segment was early replicating. The parents had normal chromosomes.

The FISH technique with the use of whole chromosome paints X and 17 demonstrated that the extra chromosomal material, which was present on the der(X), was not derived from chromosome X but from

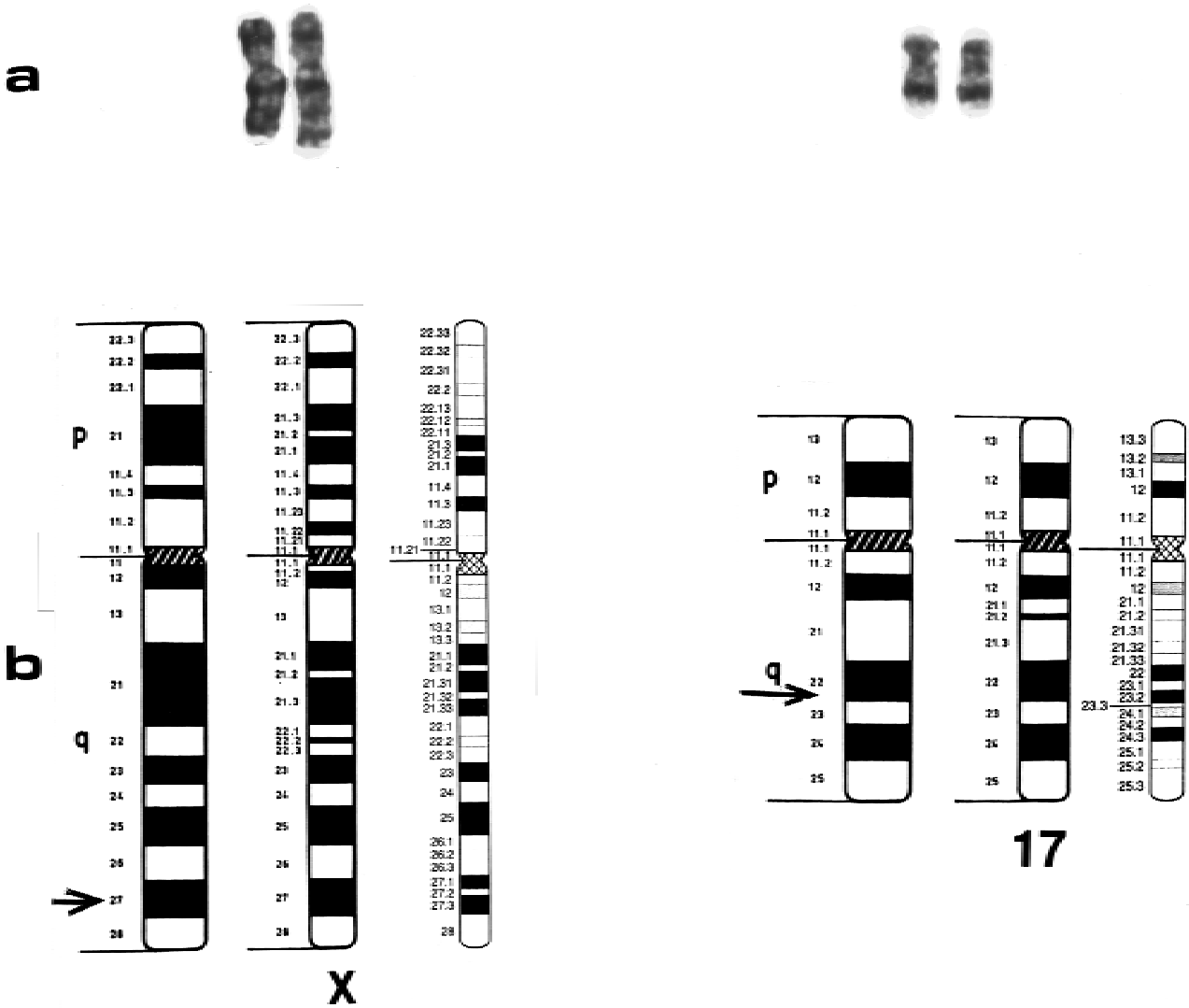

Fig. 2. **a:** Partial karyotype of the proband with GTG-banding. **b:** Ideogram of the probable breakpoint regions of the chromosomes 17 and X.

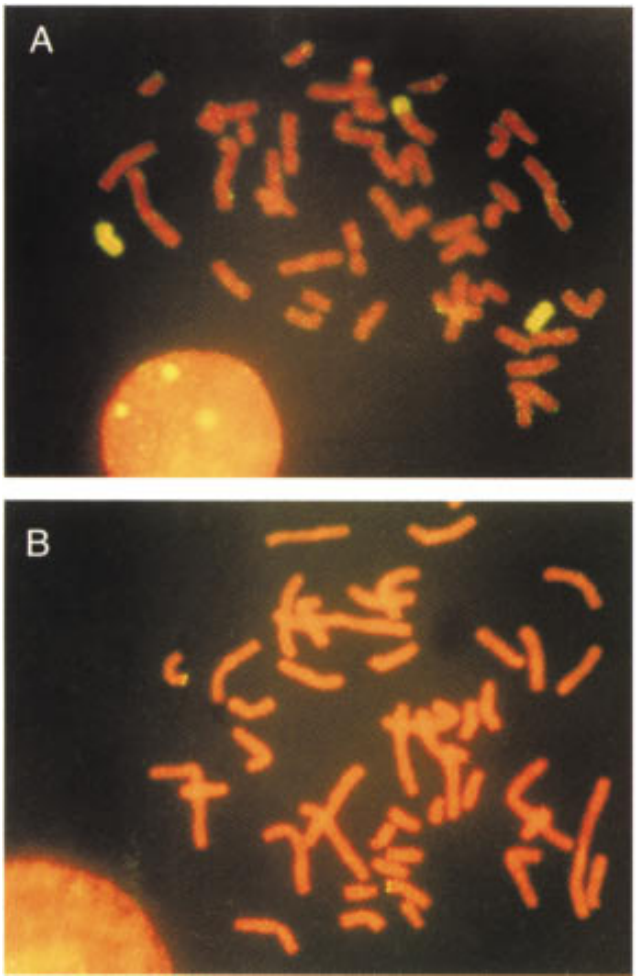

Fig. 3. FISH on metaphase chromosomes of the proband using **(A)** whole chromosome 17 paint probe and **(B)** 17p telomere cosmid probe.

chromosome 17 (Fig. 3A). The whole chromosome paint 17 did not give information about the part of chromosome 17 involved on the der(X). FISH with the 17p telomere cosmid probe (Fig. 3B) and the Miller-Dieker cosmid/chromosome 17 alpha-satellite probes gave no signals on the der(X). Therefore, it was concluded that the extra material did not belong to 17pter or to the centromere region of chromosome 17. FISH technique with the combination of RHG and high resolution GTG banding demonstrated the following karyotype: 46,X,der(X),t(X;17)(q27;q22) de novo (Fig. 2b).

Proximal chromosome Xq microsatellites showed two copies of the chromosome with one paternal and one maternal allele present, whereas three distal microsatellites showed non-inheritance of a paternal allele, thus indicating that a partial monosomy X was present (Table III, Fig. 4b). This also showed that the chromosome X part of the derivative chromosome was of paternal origin. The breakpoint on chromosome X was found to be between markers DXS1210 and DXS1227 (Table III). A microsatellite at the G6PD locus was not informative, but it should be noticed that the enzyme activity in the proposita was only 10% of the normal value, which can be explained by inheritance of a paternal X chromosome with partial deletion of distal Xq and of a maternal X chromosome carrying a mutation in the G6PD gene (the mother had partial G6PD deficiency, whereas the father had normal value). From the informative markers on chromosome 17, we found the proximal part of the chromosome to be represented with two copies, whereas the distal part of 17q was represented with three copies by dosage analysis (Table III, Fig.4a). The origin of the supernumerary allele was maternal, thus indicating that there was a partial trisomy of chromosome 17 and that the chromosome 17 part of the derivative chromosome was of maternal origin. The breakpoint on chromosome 17 was found to be between markers D17S806 and D17S788 (Table III).

DISCUSSION

Duplication 17q has been associated with a clinically recognizable syndrome, which is characterized by psychomotor retardation, short stature, microcephaly, frontal bossing, temporal retraction, narrow palpebral fissures, flat nasal bridge, long philtrum, cleft palate, large mouth, thin upper lip, low-set and malformed ears, brachyrhizomelia, hexadactyly, and hyperlaxity of limb joints. In addition, cardiac and cerebral anomalies are frequent [Grouchy and Turleau, 1982; Naccache et al., 1984]. We have summarised the clinical findings from the previously published reports in Table IV.

The distal one-third of 17q (17q23-qter) was the duplicated segment common to most of the previously reported cases, as noted earlier. Associated deletions, including the terminal segments of 21q, 21p, Xp, 5p, 4p, 3p, 12p, 12q, 11q, had little effect on the phenotypes. However, the case of Cotter and Stewart [1990] had a clinical picture of monosomy 9p and the cases of Greenberg et al. [1986] and Kingston et al. [1996] had a clinical picture of Miller-Dieker syndrome despite the concomitant existence of partial trisomy 17q23-qter. Therefore, it appears that partial trisomy 17q23-qter is largely responsible for the dup(17q) syndrome. The additional anomalies in the patient of Gallien et al. [1981], which included severe ossification defects of the skull, colobomas of both irides, a large "buffalo hump,"

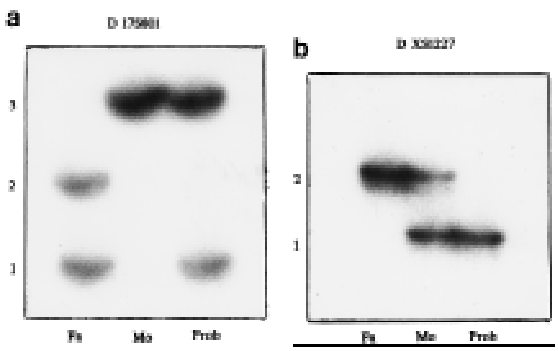

Fig. 4. DNA polymorphism analysis by PCR amplification of microsatellites in the proband and parents. FA = father, Mo = mother, Prob = proband. **a:** D17S801 demonstrating double dosage of maternal 17q alleles in the proband. **b:** DXS1227 demonstrating the absence of paternal Xq allele in the proband.

TABLE IV. Summary of Clinical Findings From Previously Published Reports of Partial Trisomy 17q Compared to Our Patient

	Published reports (number of patients = 30)				Our patient
Sex	m = 15/30 f = 15/30				f
Findings	Positive	Negative	Not described or unclear	Not relevant	
Short stature	22	0	8	0	+
Psychomotor retardation	24	0	0	6	+
Hypotonia	8	3	17	2	+
Microcephaly/large anterior fontanelle	16/7	1/0	13/21	0/2	–/+
Frontal bossing	18	2	10	0	+
Bitemporal narrowing	17	2	11	0	+
Facial/cranial asymmetry	13	6	11	0	+
Widow's peak	7	6	17	0	+
Hypertelorism/broad nasal bridge	12/1	2/3	16/26	0	+/+
Upslanted/downslanted palpebral fissures	4/3	12/2	14/25	0	+/–
Epicanthus	12	6	12	0	–
Flat nasal bridge/broad nose	15/2	4/0	11/28	0	+/+
Poorly delineated philtrum	4	0	26	0	+
Wide mouth/thin upper lip	9/10	5/0	16/20	0	+/+
Down-turned corners of the mouth	11	3	16	0	+
Cleft lip and (or) palate/bifid uvula	10/2	9/0	11/28	0	–/–
Highly arched palate	13	7	10	0	–
Micrognathia	17	5	8	0	+
Low set ears	17	2	11	0	+
Malformed ears	6	0	24	0	+
Short neck	15	5	10	0	+
Webbed neck	14	6	10	0	+
Low posterior hairline	16	2	12	0	+
Kyphoscoliosis	8	0	20	2	–
Widely spaced nipples	13	2	13	2	+
Cryptorchidism	8	2	4	16	
Proximal limb shortness	15	4	11	0	+
Polydactyly of hands and/or feet	11	8	11	0	–
Syndactyly of fingers and/or toes	10	8	12	0	–
Hyperlaxity of limb joints	9	3	16	2	–
Hirsutism	4	0	26	0	+
CNS abnormalities	11	2	17	0	+
Ophthalmological problems	4	0	24	2	+
Heart defects	13[a]	4	13	0	–
Kidney abnormalities	8	5	17	0	–
Gastrointestinal abnormalities	7	0	23	0	–
Genital abnormalities	8	0	22	0	+

[a]Including three cases with heart murmur.

omphalocele, and labia majora with the appearance of scrotal folds, were most probably due to a larger duplicated segment (17q21-qter). It seems from the previous clinical reports that duplication 17q predisposes to midline defects. CNS malformations ranging from holoprosencephaly to Dandy-Walker defect, as well as oral clefting, cardiac septal defects, omphalocele, and absent vagina were found. These findings are in agreement with the postulate of Opitz and Gilbert's [1982] that midline development is less buffered than that of paramedian structures.

In our case, the autosomal segment 17q22-qter, translocated onto the inactivated der(X), was always early replicating. This indicates that the multiple abnormalities of our patient actually represent a partial trisomy 17q syndrome. In unbalanced X-autosomal translocations, the translocated X chromosome is usually inactivated [Geerkens et al., 1994; Hagemeijer et al., 1977]. It is possible that the extension of the inactivation from the translocated X, by a spreading effect would reduce or even suppress the chromosomal disequilibrium. It is generally known that in the presence of a structural abnormality of the X chromosome, inactivation could occur at random, but usually is followed by a cellular selection favoring the better genetic balance. In our case the abnormal X chromosome is inactivated in blood, but it is unknown whether it is inactivated in other tissues. According to Hagemeijer et al. [1977], the inactivation pattern observed in one tissue is not necessarily characteristic of the whole individual.

In our case the use of FISH in combination with molecular analysis with polymorphic microsatellite DNA markers identified the breakpoints of the derivative chromosome between D17S806 and D17S788 for chromosome 17 and between DXS1210 and DXS1227 for the X chromosome. According to the molecular analysis, the origin of the abnormal X chromosome was paternal, whereas the origin of the duplicated part of chromosome 17 was maternal. The unbalanced translocation between the paternal X and the maternal chromosome 17 is therefore suggested to be due to a postzy-

gotic error, possibly a translocation in a cell with trisomy 17 of maternal origin and with subsequent loss of the reciprocal product of the translocation. It is interesting that the translocated 17q segment is not inactivated. This could be due to the suggested postzygotic origin of the translocation, perhaps after X inactivation has taken place. The present case makes a new addition to the expanding category of mitotically derived chromosome abnormalities, as previously described in some cases of trisomy 21 [Antonarakis et al., 1993], trisomy 18 [Fisher et al., 1993], trisomy 8 [Grigoriadou et al., 1995; James and Jacobs, 1996], homologous Robertsonian translocations and isochromosomes [Blouin et al., 1994; Robinson et al., 1994], and disomy/trisomy mosaicism [DeBrasi et al., 1995; Pangalos et al., 1994; Robinson et al. 1995]. Apparently, our case is the first non-Robertsonian translocation in which this kind of observation has been made.

To the best of our knowledge, this is the first case of partial trisomy 17q that is identified by molecular analysis and the second case that is identified by FISH. The first such case was reported by Kingston et al. [1996] in a male with Miller-Dieker syndrome and a duplication 17q25-qter, owing to a familial chromosome 17 inversion. Our patient is also the third published case in which the partial trisomy probably is due to a postzygotic error. The first such case was reported by Serotkin et al. [1988] in a female infant with multiple anomalies who was mosaic for duplication 17q21-qter, owing to a direct tandem duplication. The second case was reported by King et al. [1991] in a female infant born after prenatal diagnosis of mosaic partial trisomy 17q21.1-qter. However, these two cases were not studied by FISH or molecular analysis.

The patient described in this report presented with Stargardt disease, a macular degeneration of early onset, and a rapidly progressive course. This condition is genetically heterogeneous and can be transmitted as an autosomal recessive trait (one locus mapped to chromosome 1) or as an autosomal dominant trait (loci mapped to chromosomes 6 and 13) [Rosenfeld et al., 1994]. To the best of our knowledge, Stargardt disease has not been described in association with chromosomal aberrations involving chromosome 17, and we propose that a further locus for Stargardt disease may map to either the breakpoint at 17q22 or to the duplicated segment 17q22-qter.

In conclusion, cases of partial trisomy 17q including the present one show some variability in clinical expression, related to the extent of the 17q duplication. A study of more patients is needed to refine the phenotypic mapping of chromosome 17 and to correlate different clinical syndromes with the extent of the 17q duplication. It is also important that chromosomal abnormalities are studied by molecular analysis in order to discover the underlying mechanisms of formation.

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